Amendments to the Drawings

Replacement figures are being submitted. Figure identifiers have been converted to lower case letters consistent with the specification. Figure identifiers in the upper left area of certain figures have been removed; they were redundant in view of the main figure identifiers (e.g., Fig. 12a). It is believed that no new matters is being added. Applicants respectfully submit that these drawings resolve the Patent Office objections.

Attachment: Replacement sheets of all drawings

Remarks and Arguments

Reconsideration of the present application is respectfully requested in view of the above amendments and following remarks.

Information Disclosure Statement

The Examiner has noted that the A.R. Ten Cate reference did not include page 198. Applicants enclose page 198 of this reference. Applicants respectfully request that the Examiner initial the Information Disclosure Statement upon consideration of this reference.

Claim Objections

The examiner has objected to claims 7 and 9-22 for use of parentheses and multiple dependencies. Original claims 1-28 have been cancelled and new claims 29 – 67 are submitted herewith. It is believed that these new claims overcome the claim objections.

The Double Patenting Rejection

The Examiner has rejected original claims 1, 7 and 8 under the judicially created doctrine of obviousness type double patenting over claim 7 of the Cerny et al. U.S. Patent No. 6,300,062.

Original claims 1-28 have been cancelled. Without conceding the basis of the Examiner's rejection, it is believed that these new claims render the rejection moot.

The Section 101 Rejection

The Examiner has rejected original claims 1-22 as improperly claimed under Section 101.

Original claims 1-22 having been cancelled and replaced with new claims 29-67. Without conceding the basis of the Examiner's rejection, it is believed that these new claims render the rejection moot.

The Section 112 Rejections

The Examiner has rejected original claims 1-28 under first and second paragraphs of Section 112 on a variety of grounds.

Claims 6, 7, and 9-22 were rejected under 35 U.S.C. §112 1st paragraph for allegedly failing to comply with the written description requirement. The Office believes that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Patent Office took issue with the term "derivatives". To support its position, the Office relies on *University of California v. Eli Lily and Co.*, 25 USPQ2d 1601 (Fed. Cir. 1993) ("Lily," hereinafter). Applicants believe the instant case is distinguishable from Lily.

In Lily, the Federal Circuit ruled that a generic claim to all insulin DNA sequences was invalid for lack of written description, where only the rat DNA sequence was disclosed. Applicants first note that the there is nothing in Lily to suggest that the holding should be extended to proteins. Moreover, Applicants are not aware of any subsequent case that has so extended the Lily holding. Still further, unlike Lily, in this case Applicants are not claiming a broad genus of previously unknown sequences. Furthermore, for the reasons set forth below, Applicants have both demonstrated possession of the invention and have provided sufficient description of the claimed subject matter and thus have satisfied the written description requirement.

The Office appears to be concerned with the term "derivative" which is now recited in claims 37, 38, and 39.

At page 21, line 12 of the specification, the commercially available product Emdogain®, is explained to comprise enamel matrix derivatives (e.g., 30 mg/ml in propylene glycol, as described on page 24, line 34). Enamel matrix derivatives, and examples of how they are obtained, are described in detail beginning on page 6, line 1 of the specification. Also included are descriptions of the claimed proteins and their processing. It is therefore clear what is meant by enamel matrix derivatives and the claimed protein derivates of the present invention. Additionally, as the Emdogain® product, comprising enamel matrix derivatives, was used in the experimental section of the application, derivatives of enamel matrix proteins have been shown to be functional for the practice of the present invention. Thus, the inventor, at the time the application was filed, had indeed possession of the claimed invention.

Without conceding the bases of the Examiner's rejections, it is believed that all other 112 rejections have been rendered moot by the new claims.

The Section 102(e) Rejection

Claims 1-3, 5-16, 18, 19, 21 and 22-28 were rejected under 35 U.S.C. 102(e) as anticipated by Cerny et al. Cerny et al. do not supply the teachings alleged by the Patent Office.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. New independent claim 29 includes the limitation "administering to exposed vital dental pulp tissue of said mammal an active enamel substance in an amount sufficient to promote one or more of regeneration of secondary dentin or formation of reparative dentin or osteodentin".

The Patent Office has not shown where there is an express teaching of this claim limitation. The sections of Cerny et al. cited by the Patent Office do not disclose this limitation.

Cerny et al. explicitly relates to a method of promoting or provoking the mineralization of hard tissue selected from the group of bone, enamel, dentin and cementum, see page __, lines 29-32, and page 27, lines 10-13. Thus, mineralization of already existing dentin is described, not Applicant's claimed "regeneration of secondary dentin or formation of reparative dentin or osteodentin."

In one embodiment, Cerny et al. relates to a method of repairing a lesion in a tooth. The method comprises the administering of an enamel matrix polypeptide to the surface of the lesion. As previously indicated, Cerny et al. teaches that enamel matrix enables mineralization of already existing dentin. Cerny et al. is not directed to and does not teach that enamel matrix should be administered to exposed vital dental pulp tissue, as Applicant now claims, to promote one or more of regeneration of secondary dentin or formation of reparative dentin or osteodentin. Again, Cerny et al. teaches mineralization of existing dentin, not Applicant's claimed regeneration, nor Applicant's claimed administering to exposed vital dental pulp tissue as recited in the presently claimed method.

Thus, Applicant respectfully asserts that all of the present claims are not anticipated by Cerny et al. Applicants respectfully request withdrawal of the rejection.

The Section 103 Rejections

The Patent Office rejected original claims 1-3, 5-16, 18, 19, 21, and 22-28 as being unpatentable under 35 U.S.C. 103(a) in view of the U.S. Patent No. 6,300,061 (Cerny et al.). The Patent Office further rejected claims 1-19, 21 and 22 as being unpatentable over U.S. Patent No. 6,503,539 (Gestrelius et al.) in view of Nakamura et al. and Ruch et al.

Obviousness is a legal conclusion based on factual evidence. *Graham v. John Deere Co.,*. 383 US 1, 148 USPQ 459 (1966). The PTO has the burden under 35 U.S.C. §103 to establish a prima facie case of obviousness. *In re Piasecki,* 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). In order to establish the prima facie case of obviousness, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art and the knowledge of persons of ordinary skill in the art. *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-1458 (Fed. Cir. 1998).

To establish *prima facie* obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). The motivation to make the claimed invention and a reasonable expectation of success must both be found in the prior art, not the applicant's disclosure. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). The references must be considered as a whole and must suggest the desirability, and thus the obviousness of making the combination. *Hodosh v. Block Drug Col, Inc.,* 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986); MPEP § 2141.

If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

A. Rejections over Cerny et al.

The present invention is based on the discovery that administering active enamel substance to vital dental pulp causes *regeneration* of certain types of dentin. See e.g., page 5, lines 1-17 of Applicants' disclosure.

The Patent Office states that Applicants' claims are obvious over Cerny et al. because Cerny et al. teach mineralization of certain hard tissues (e.g., dentin).

Cerny et al. disclose mineralization of pre-existing dentin by application of a polypeptide. Cerny et al. do not disclose or suggest application of the polypeptide to vital dental pulp, nor that such application would cause Applicant's claimed regeneration. Therefore, there is no basis for the Examiner's conclusion that it would be obvious to apply enamel matrix to dental pulp because there is no teaching in Cerny et al. of this application or that this application will have the claimed effect.

B. Rejections over Gestrelius et al. in view of Nakamura et al. and Ruch et al.

As discussed above, new independent claim 29 requires the administration of an active enamel substance to exposed vital dental pulp tissue for regeneration and/or formation of secondary dentin, osteodentin and/or reparative dentin. None of the three references taken alone or combined, teach Appilcant's claimed method.

Nakamura et al. disclose a study of the synthesis and pathways of amelogenin proteins during development of first molar teeth in mouse fetuses. The study shows that amelogenin proteins secreted from preameloblasts can be identified along cell processes and cell surfaces of odontoblasts adjacent to forming mantle dentine extracellular matrix prior to biomineralization. However, the Nakamura study is simply concerned with the location of the amelogenin proteins during tooth development, which would include the formation of primary dentin, and does not disclose or indicate that the amelogenin proteins would be involved in the formation of secondary or reparative dentin or osetodentin. Rather, as is evident from the last line of the abstract, even in this context of initial tooth formation, the biological function of the amelogenin proteins, translocated to the odontoblasts prior to biomineralization, is unknown.

Therefore, Nakamura et al. does not teach or suggest the subject matter of the present claims.

Applicants respectfully disagree with the Patent Office's statement that a skilled artisan would have been motivated to mimic the developmental biological processes of dentin formation by using enamel substances for two reasons. First, as stated above, Nakamura et al. state that these proteins serve an unknown biological process. Therefore, without knowing the function of these proteins, it is doubtful that a skilled artisan would have been motivated to apply these proteins to obtain a particular result. Second, the Patent Office has not pointed to any motivation to apply these proteins to exposed vital dental pulp tissue in Applicant's claimed method.

Neither of the other two references, Gestrelius or Ruch, cure the deficiencies of Nakamura.

For at least these reasons, Applicants respectfully submit that the Patent Office has not met the burden of the prima facie case, and respectfully request reconsideration and allowance of all claims.

Reconsideration

It is believed that all claims of the present application are now in condition for allowance.

Reconsideration of this application is respectfully requested. If the Examiner believes that a teleconference would expedite prosecution of the present application the Examiner is invited to call the Applicant's undersigned attorney at the Examiner's earliest convenience.

Any amendments or cancellation or submissions with respect to the claims herein is made without prejudice and is not an admission that said canceled or amended or otherwise affected subject matter is not patentable. Applicant reserves the right to pursue canceled or amended subject matter in one or more continuation, divisional or continuation-in-part applications.

To the extent that Applicant has not addressed one or more assertions of the Examiner because the foregoing response is sufficient, this is not an admission by Applicant as to the accuracy of such assertions.

Please grant any extensions of time required to enter this response and charge any fees in addition to fees submitted herewith that may be required to enter/allow this response and any accompanying papers to our deposit account 02-3038 and credit any overpayments thereto.

Respectfully submitted,

Date: Jan 3, 2006

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heterogeneous group of gene-specific, low-molecular-weight proteins known as *amelogenins.* The remaining 10% of enamel protein consists of *enamelin, tuftelin,* and *amelin.*

Enamel Proteins

The nature and behavior of enamel proteins are long-standing and intriguing questions. Amelogenins are of a heterogeneous group of low-molecular-weight (20 to 30 kDa), hydrophobic proteins, rich in proline, histidine, and glutamine. This heterogeneity is brought about in three ways: The genes responsible for transcribing amelogenin are found on both X and Y chromosomes, and, as these two genes are not 100% homologous, a sexual heterogeneity exists at the outset, which means that in the female 10% of the total transcribed amelogenin derives from the Y chromosome. The functional significance of this sexual dimorphism is not known. Second, the amelogenin gene contains at least seven exons, which can be spliced in numerous ways to produce mature mRNAs that may include all seven exons or lack certain exons or parts of exons. Alternatively spliced forms are not found in great quantity, but they do exist, and the functional significance of the need to have alternatively spliced amelogenins is not known. The bulk of amelogenin secreted is a 25-kDa parental amelogenin derived from the gene located on the X chromosome. Once it is secreted, the third mechanism producing heterogeneity comes into play. This involves degradation of parental amelogenin by proteolytic enzyme activity into lower-molecular-weight proteins, of which tyrosine-rich amelogenin polypeptide (TRAP) and lysine-rich amelogenin polypeptide (LRAP) are significant because they constitute the bulk of the final organic matrix of enamel (Fig. 10-2).

Tuftelin is a 45-kDa, acidic phosphorylated glycoprotein whose gene has been cloned and localized to chromosome 1.

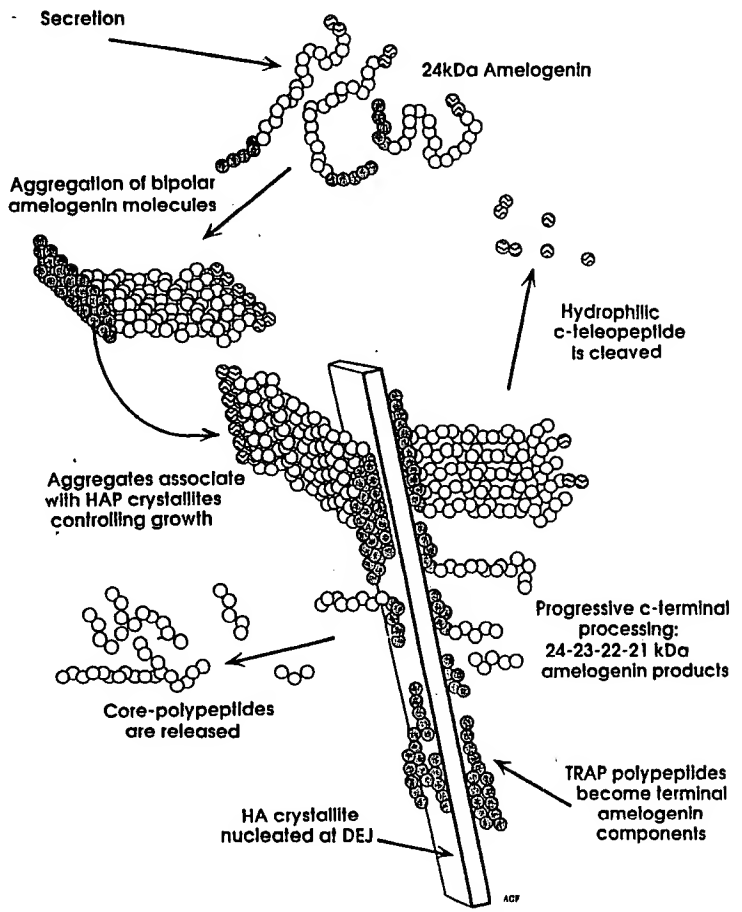

Figure 10-2 Hypothetical scheme for amelogenin-mediated enamel biomineralization. (Courtesy Dr. A Fincham.)